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ABSTRACT

This edition, the sixth in the series of annual reports, is a nontechnical summary updating developments in marihuana research with selected references from the fifth edition. Areas of discussion include: (1) nature and extent of marihuana use in the United States; (2) marihuana use among high school seniors; (3) an overview of use trends; (4) predicting marihuana use; (5) chemistry and metabolism of cannabis; (6) animal research; (7) human effects; (8) special health problem areas; (9) overseas chronic user studies; (10) psychopathology; (11) complex psychomotor performance in driving and flying; (12) tolerance and dependence; (13) therapeutic aspects; (14) future research directions. Progress in the marihuana research programs has underscored the need for more subtle understanding of marihuana use and its possible implications. List of references in included. (MM)

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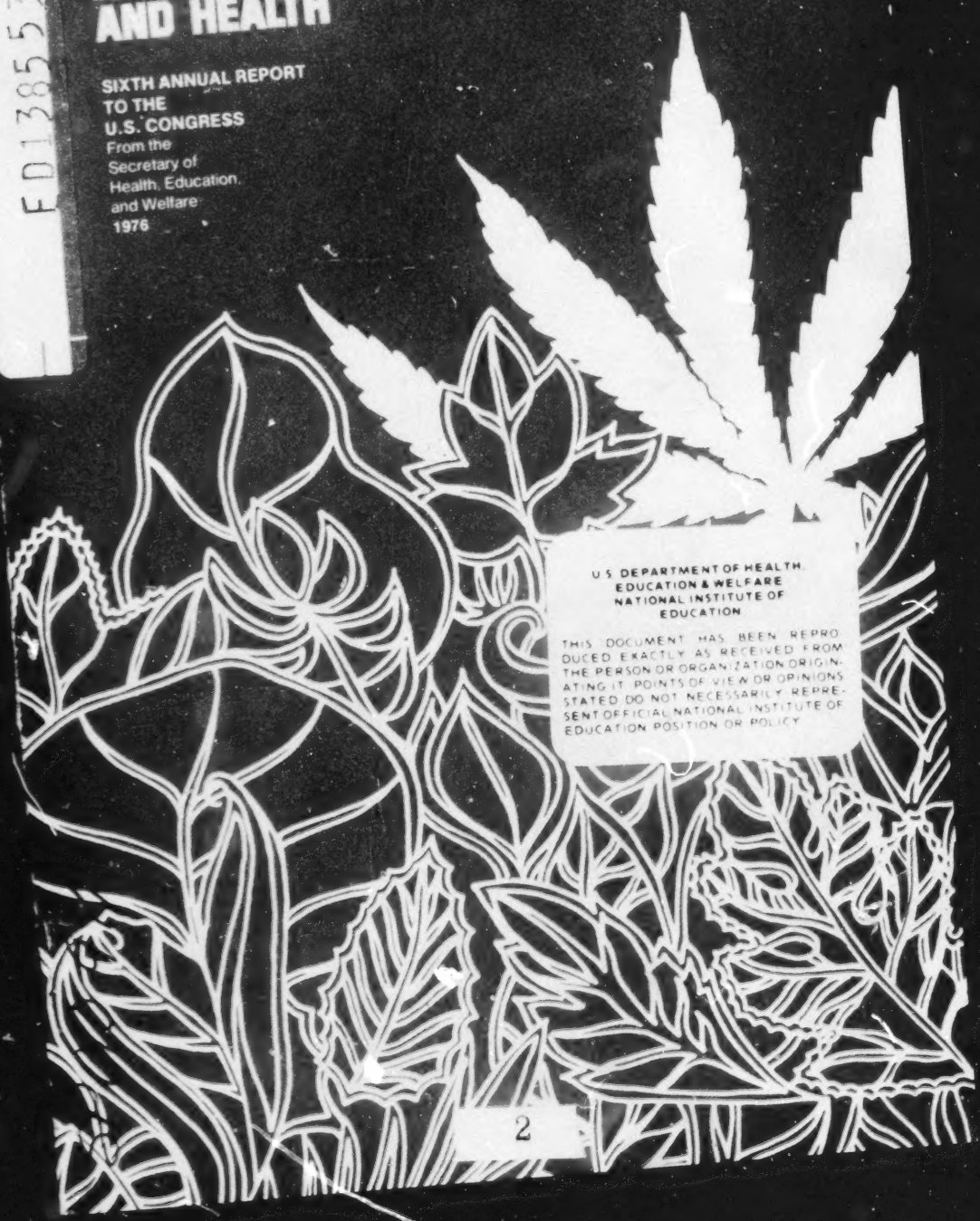
MARIHUANA AND HEALTH

SIXTH ANNUAL REPORT TO THE U.S. CONGRESS
From the Secretary of Health, Education, and Welfare
1976



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MARIHUANA AND HEALTH

Sixth Annual Report
to the U.S. Congress
From the Secretary of
Health, Education, and Welfare
1976

National Institute on Drug Abuse
11400 Rockville Pike
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Dr. Robert C. Petersen wrote the Report and, as senior editor, had primary responsibility for its overall preparation.

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FOREWORD

This report, like its five predecessors, summarizes our growing, though still limited, knowledge of the health consequences of marihuana use. To the over simplified question, "Is marihuana use safe?", we can offer a simplistic, but unequivocal, "No." There is good evidence that being "high" -- intoxicated by marihuana -- impairs responses ranging from driving to intellectual and interpersonal functioning.

It is hardly surprising that marihuana is not "safe" in any absolute sense for no drug is or can be under all conditions of use. Many substances as diverse as alcohol, tobacco, cyclamates and red dye No. 2, do not harm all users, but may be fraught with adverse health consequences for a significant number of them. Marihuana, too, can be hazardous even when used occasionally.

We now know that marihuana intoxication poses a significant threat to highway safety in much the same way that alcohol does. The exact size of that threat remains a matter for conjecture. Many marihuana users report driving while intoxicated and since we know driving skills are impaired under those circumstances, the problem is real.

A related source of concern is the increasing number of Americans who use marihuana on a daily or near daily basis. Just over 8 percent of the nation's 1976 high school graduates reported virtually daily marihuana use. The number of 1976 graduates using marihuana on that basis was 40 percent greater than the number making equally frequent use of alcohol.

To date, most American marihuana users smoke relatively low potency material and only occasionally. The apparently benign picture presented by that type of use -- aside from possible hazards related to functioning while intoxicated, few other specific health hazards have been definitively identified -- may change if more frequent use of stronger material becomes more common. If laboratory findings of possible effects on the body's immune response, endocrinological functioning and cell metabolism prove to have serious clinical implication, marihuana's persistence in the body may make even episodic use risky.

More realistic than the question of marihuana's absolute safety under all conditions of use are two questions:

1. What is the health risk at present and anticipated levels of use in the United States?

2. What are the specific areas of health hazard and who is at risk?

Neither of these questions can be satisfactorily answered at present. The increasing availability in the United States of large numbers of individuals who have used marihuana over a period of several years makes it increasingly possible to do the type of large

scale study that could previously only be done abroad under quite different cultural conditions. Such studies are being planned. Other, more specific research is planned to resolve the questions raised by the laboratory findings across a broad spectrum.

This report emphasizes the large and apparently growing number of Americans who have used marihuana. While this finding deserves emphasis, it is equally important to recognize that more than half of the Americans who have used marihuana have quit using it. Even larger is the number of people who say that they have not used and have no intention of using marihuana regardless of the legal status of the drug.

In recent years, those who have had to deal with legal substances as diverse as alcohol and red dye No. 2 have had to face the fact that these agents are not "safe" under all circumstances and that whatever social policy is adopted concerning their availability must take this disquieting fact into consideration. Similarly, in the area of illicit drugs, we now recognize that many users suffer no apparent ill effects. The realization that significant numbers of users of legal substances may suffer ill effects at the same time that many users of prohibited substances have no problems with their use, has strained our national capacity to deal rationally with the fundamental social policy issues involved. We hope that this report describing the current state of our knowledge of marihuana's health consequences continues to contribute to a better understanding of the complexity of this important social issue.

Robert L. DuPont, M.D.
Director
National Institute on Drug Abuse

MARIHUANA AND HEALTH — 1976

Introduction

This edition of Marihuana and Health is the sixth in the series of annual reports from the Secretary of Health, Education, and Welfare to the Congress as required by Title V of Public Law 91-296. Like its predecessors, this report attempts to provide an objective answer to the question, "What are the health implications of marihuana use for Americans?" This edition is considerably briefer than earlier reports because it is addressed to a general audience rather than being a summary of the scientific literature for the technically trained.

The reasons for these changes are several. When the first report was issued nearly six years ago a publication was needed to review the scientific literature for public policy deliberations and to provide a more detailed review for the technically trained. The needs of the scientific community for summaries of the now extensive research literature are currently being met from multiple sources. Continued availability of the Fifth Report (105) together with this summary of more recent developments will provide a relatively complete review of our current knowledge. In addition, the sheer bulk of the material involved, given its technical nature, makes the previous dual purpose report increasingly impractical for general distribution. Thus, the present report is in the nature of a non-technical summary updating developments of the past year with selected references from the fifth edition.

OVERVIEW AND PERSPECTIVE

Marihuana use, which first began to involve significant numbers of American youth in the 1960's, generally continues to increase. Most users reported occasional use of low potency material. However, more regular use of stronger materials has increased. Last year 1 in 12 high school seniors nationwide reported using marihuana 20 or more times per month. In peak using groups, figures are still higher. Among males 20-24 years old, about 1 in 10 uses on a daily basis. If we restrict our analysis to those in this age group who have ever used, nearly one in five (17 percent) does so daily.

The amount of research on chronic use remains modest. This is especially true when considered in the light of the estimated 36 million Americans who have tried the drug and the nearly 15 million who used it within the month preceding the last national survey. While three carefully controlled overseas studies have compared long term user populations to non-using populations, the actual number of matched user/non-user pairs was small (a total of 117 users) due to the complexity of the research design. There is considerable evidence from experience with other drugs that many years of use by substantial numbers is required for the implications

of widespread drug use to surface. Moreover, the small samples studied thus far would probably not have revealed some of the most serious adverse consequences of any habit, as illustrated by cigarette smoking. Laboratory research in the United States has been largely restricted to young males in good health as have larger U.S. studies of psychosocial aspects of use. Marihuana's effects on those in poor health or older people and on females have not been adequately examined. Despite these obvious limitations to our knowledge, many have interpreted the preliminary findings as indicative that "marihuana is safe."

Preliminary marihuana research evidence has been eagerly sought, its limitations too frequently ignored and its implications often overdrawn to provide support for one or another side of the debate on social policy. Changes in social policy dictated by the necessity of finding a wiser, more workable drug policy concerning personal use and possession are in danger of being interpreted as indicating that marihuana is without significant hazard.

While the picture regarding marihuana use is far from complete, it should be emphasized that there is good evidence that use is by no means harmless. Such behaviors as the operation of a motor vehicle or complex psychomotor performance are clearly impaired by marihuana use in a manner somewhat similar to that of alcohol use. A variety of both clinical and experimental observations makes it seem quite likely that heavy use of smoked marihuana will impair lung function and may result in consequences similar to those of cigarette smoking.

Marihuana is most widely used by adolescents and young adults during critical stages in their personality development and while developing intellectual and psychosocial skills. To what extent, if any, chronic intoxication affects development is still unknown. While the percentage of the population which uses heavily on a daily basis is still a small minority even in this group, any serious consequences of use may well be expected to have implications for extended periods of their lives.

The quest for a rational social policy has resulted in a continuing demand for a simple answer to the question, "Is marihuana harmful?" Unfortunately, the apparent simplicity of both the question and the desired answer are deceptive; both are complex.

A series of laboratory findings concerning the possible adverse impact of marihuana on such areas as the body's immune response, basic cell metabolism and other areas of functioning has not yet been adequately explained. Although it is possible that some of them may ultimately prove to be without clinical significance, the possible hazards dictate a degree of caution in prematurely concluding that we now know enough about the dangers of cannabis use. Unlike alcohol in which many of the implications of chronic use are well documented (and from a public health standpoint, serious), similar parameters of risk for cannabis use have not yet been adequately explored.

As marihuana use escalates it is highly probable, for example, that such use will come to include more individuals with already impaired physical or psychological functioning for whom use and particularly regular use may have quite different implications than occasional use by those in optimal health. Evidence on cardiac patients cited over the past two years is one example. Similarly, the implications of use for marginal members of the society or for those having greater problems with coping or less skills for doing so, may be quite different from those of the more competent, advantaged student user.

Research over the past several years has markedly expanded our knowledge of many of the effects of marihuana and its patterns of use both here and abroad. Despite this rapid expansion in our knowledge much remains to be learned, especially about the implications of chronic use. Most therapeutic drugs are used in pure forms for a limited duration of time, for a specific purpose, in controlled doses and often under medical direction. Marihuana, by contrast, is quite variable in potency, not uncommonly used regularly over extended periods of time and with no supervision to alert the user to possible adverse effects. Given the widespread patterns of use, it is critical that we continue to define the parameters of risk both when used alone and in combination with other drugs. Now that there are significant numbers of Americans who have been using for periods of several years or more it is desirable that we study use in a manner parallel to the overseas studies which have been conducted, but on a much larger scale. If serious hazards are anticipated, it is essential that they be discovered soon. With the present trend toward increasing use, early detection of more serious health implications may discourage marihuana use before it becomes as firmly entrenched in U.S. social customs as are alcohol and tobacco use.

NATURE AND EXTENT OF MARIHUANA USE IN THE UNITED STATES

Marihuana use among the general U.S. population has not appreciably changed since the issuance of the Fifth Marihuana and Health Report (105). Concentration continues among adolescents and young adults as shown by the most recent national survey (2) which found the largest percentages of those who had "ever used" and now using (defined as use within the month preceding the survey) among the 18-25-year-olds. A majority (53 percent) of this age group has used marihuana at some time; a quarter of the sample within the past month.

Among older age groups (over 25), the percentage of those who have ever used drops precipitously. Similarly, of those adults who have used cannabis, the percentage reporting current use is considerably lower than that of younger groups. For example, approximately one-third (36 percent) of the 26-34-year-olds report having tried marihuana as compared to one-half of the 18-25-year-olds. But less than one-third of the 26-34 age group who have ever used report current use (within the month preceding the survey), while about half of the 18-25 group who have ever used marihuana are current users. In the over 35 age group about 1 in 20 reports having tried the drug; but only 1 in 6 of those who had ever used, reported current use.

Among adolescents questioned in the National Survey, the 12-13-year-olds reported little use: 6 percent of this group report having ever used, half of these within the past month. Among 14-15-year-olds, one in five has used but in the 16-17-year-old group twice as many (two in five) have tried marihuana. For all youth groups (12-17-year-olds) about half of those who have ever used are current users.

When the survey results are analyzed for sex differences, twice as many men as women over 18 (29 percent vs. 14 percent respectively) have had experience with the drug. By contrast, the sex differences are less marked among 12-17-year-olds who have ever used (26 percent of males vs. 19 percent of females). Once again, about half of those who have ever used report that they are currently using.

Tables 1 and 2 provide National Survey data for the years 1971 through 1976 on marihuana use by adults (those over 18) and by youth (the 12-17 age group). When asked about their plans for future use of marihuana, one in five youths (the 12-17 age group) anticipated possible future use. By contrast, one in three of those 18-25 (the peak using age group) anticipated future use, while only one in ten of those over 26 had similar expectations.

When comparisons are made on a national basis between current use of marihuana and use of cigarettes and alcohol, use of the latter drugs is considerably greater than that of marihuana. Among youth, one-third reported having drunk alcohol in the preceding month, one-quarter reported use of tobacco and one-eighth marihuana use. While 60 percent of the adults reported alcohol use in the preceding month

Table 1

MARIHUANA USE AMONG ADULTS, 1971-1976

	% Ever Used				% Current Use**			
	1971	1972	1975	1976	1971	1972	1975	1976
All adults	15	16	19	21	5	8	7	8
Age:								
18-25	39	48	53	53	17	28	25	25
26-34	19	20	29	36	5	9	8	11
35+	7	3	4	6	--*	--*	--*	1
Sex:								
Male	21	22	24	29	7	11	9	11
Female	10	10	14	14	3	5	5	5

*Less than 0.5%
**Used during last month

Table 2

MARIHUANA USE AMONG YOUTH, 1971-1976

	% Ever Used				% Current Use*			
	1971	1972	1975	1976	1971	1972	1975	1976
All youth	14	14	23	22	6	7	12	12
Age:								
12-13	6	4	6	6	2	1	2	3
14-15	10	10	22	21	7	6	12	13
16-17	27	29	39	40	10	16	20	21
Sex:								
Male	14	15	24	26	7	9	12	14
Female	14	13	21	19	5	6	11	11

*Used during last month

---

and 40 percent had smoked tobacco during that same period, 10 percent reported current marihuana use.

A continuing concern with respect to cannabis use is a possible shift toward the use of higher potency cannabis. One type, hashish, is widely available in the United States where it, too, has been most widely used by young adults. Nearly one-third (29.2 percent) of the 18-25-year-olds reported ever using hashish, with about one-fifth of these reporting use during the month preceding the survey. Among the 18-25 age group, 19.5 percent reported that he or she "definitely" or "might" use hashish in the future. This contrasts with the less than one in ten for those aged 12-17 and less than 3 percent of adults 26 and over who anticipated future use of hashish. It is not known, however, whether users preferred the hashish to less potent forms of cannabis given a choice. (Hashish, a concentrated resin of cannabis, contains on the order of five to ten times as much of marihuana's principal psychoactive ingredient as marihuana itself. Typical marihuana in the United States contains 1-2 percent THC, as compared with hashish which has as much as 10 percent THC.)

Marihuana Use Among High School Seniors

In addition to the samples of youth mentioned with the National Survey results, an annual national survey of high school seniors on life style and values as related to drugs has been started (40). This study is significant because it represents an attempt to examine the change in attitudes and behavior over time during the critical years of late adolescence and young adulthood. Since this survey taps both drug using behavior and attitudes toward drugs, it will hopefully provide information for predicting future trends. Moreover, the large national, random sample (13,000 representative high school seniors) makes it unusually sensitive to recent trends in drug use among this age group. Although only the classes of 1975 and 1976 have been studied thus far, the results are of considerable interest. The proportions which had ever used marihuana increased from 47 percent in the Class of '75 to 53 percent in the Class of '76. Those who had used within the month preceding the survey had also increased from 27 percent to 32 percent. Because of the large samples involved, it is unlikely that either of these increases is a statistical artifact. Another finding of note was that the percentage of seniors who had used marihuana 20 or more times in the preceding month (8 percent) exceeded the percentage who had used alcohol that many times during the same period (6 percent).

The seniors' attitudes toward marihuana had also shifted. While 55 percent disapproved of occasional marihuana use in the Class of '75, only 48 percent felt that way in the Class of '76. While slightly over one-quarter of 1975 seniors felt "using marihuana should be entirely legal," one-third of the '76 class shared this view (27.4 percent vs. 32.6 percent). An additional quarter (25.5 percent) of the '75 class felt use "should be a minor violation -- like a parking ticket -- but not a crime." This proportion increased to

29.1 percent in the '76 Class. Only a quarter of the seniors surveyed in 1976 felt that marihuana use "should be a crime." On the issue of whether sale of marihuana should also be legal, if use were legalized, nearly two-thirds (63.2 percent) of the '76 class felt it should be as contrasted with 52.3 percent holding this belief during the Class of '75 survey. Half (49.9 percent) of the seniors would, however, restrict such sales to adults; only 13.3 percent supported the idea of unrestricted sales.

One local survey of junior and senior high school students in San Mateo County is of interest because it has been conducted annually (since 1968) in a county with unusually high rates of drug use (4). As early as 1968 nearly half (48 percent) of this Northern California county's 12th graders had used marihuana 1 or more times in the previous year, over half of these 10 or more times. By 1971, 59 percent of the 12th graders had tried marihuana in the preceding year. Two out of five of this group (43 percent) had used ten or more times that year while one in three (32 percent of 12th graders) had used fifty or more times that year.

Among ninth graders, one in four (27 percent) had used marihuana in the year preceding the 1968 survey. Of those in the ninth grade who were users, half (or 14 percent of the total) had used marihuana 10 or more times that year. By 1971, nearly half (44 percent) of the ninth graders had tried marihuana the previous year, again, about half of the users on 10 or more occasions. Slightly less than one in five ninth graders (17 percent) had used marihuana on fifty or more occasions that year. Since 1971 the figures for use have been fairly consistent for both the younger and older groups at all levels of use. About half of the ninth graders reported some use in the previous year. Of these, approximately 60 percent had used marihuana 10 or more times and approximately 1 in 3 of the user group had used as many as 50 times in the preceding year. The exact figures tracing these trends are to be found in Table 3.

Notably, in this high drug use county, male 12th graders who had used marihuana at least 50 times in the year preceding the Spring, 1976 survey exceeded the number who had made use of tobacco that often (30.0 percent had used marihuana 50 or more times compared to 23.5 percent who had used tobacco that frequently). For girls roughly the reverse was true; about one-third had used tobacco fifty or more times versus one in five who had used marihuana that often. Among both boys and girls in the 12th grade, alcohol use on 50 or more occasions only modestly exceeded marihuana use (among boys the figures for 50 or more occasions of alcohol use was 37.6 percent vs. 30.0 percent for marihuana; for girls, comparable figures were 26.2 percent vs. 21.3 percent).

The above figures for San Mateo County are of interest because they provide some evidence that the use of marihuana in this high use county may have reached a plateau and is even diminishing for some of the other drugs (amphetamines, barbiturates, LSD and tobacco use by males). Since California has elected to decriminalize the personal possession of small quantities of marihuana, subsequent

Table 3

PERCENTAGE OF MARIHUANA USE AMONG MALE SAN MATEO COUNTY HIGH SCHOOL STUDENTS

	One or more uses in past year		Ten or more uses in past year		Fifty or more uses in past year	
Grade:	9th	12th	9th	12th	9th	12th
1968	27	45	14	26	NA	NA
1969	35	50	20	34	NA	NA
1970	34	51	20	34	11	22
1971	44	59	26	43	17	32
1972	44	61	27	45	16	32
1973	51	61	32	45	20	32
1974	49	62	30	47	20	34
1975	49	64	30	45	20	31
1976	48	61	27	42	17	30

results from this annual survey may serve as one measure of the impact of this legal change on adolescent use. Thus, this county may provide some indication of future trends in other areas of the U.S. where drug use is still climbing or where laws are being revised.

A study of drug use by young adult males 20-30 years old conducted in late 1974 and early 1975 (reported in the Fifth Marihuana and Health Report, 105) has now become available as a monograph in the National Institute on Drug Abuse's Research Monograph series (73). Findings for this age group are generally quite consistent with data from other studies. Correlates of drug use such as marital status, employment and sizes of community of residence are also reported.

Use Trends -- An Overview

Use of marihuana has markedly increased since the late 1960's when interest in the drug first began to accelerate. Initially, use was confined to a small minority characterized by a counterculture orientation and for whom it was a symbol of opposition to the "establishment." Users now come from a broad cross section of U.S. youth although use, particularly regular use, remains more common among the less conventional. In at least one age group (young adults from 18-25) a majority have at some point tried the drug. Among adolescents and adults under 25 about one-half of those who have ever tried marihuana continue to use it at least occasionally. National statistics regarding marihuana use can, however, be misleading. Average trends can mask significant local and regional differences. Use rates continue to be positively related to sex (male use generally exceeds that of females), age (young adult rates higher than either younger or older age groups), size of community (larger communities report greater use than smaller) and region (higher in West and Northeast than in the South or Midwest). Over the past several years many of these differences have diminished but between 1975 and 1976 there were few changes. In one county of high use in which surveys have been consistently conducted, use by high school students as early as 1968 already exceeded that on most college campuses. Thus, the more modest use picture conveyed by the national data may mask considerably greater use among certain geographic and demographic subgroups.

In spite of the rapid increase in cannabis use over the past decade, its use is still largely confined to the young. Past age 25, experimentation with marihuana and its continuing use becomes increasingly less common. For individuals over 35, marihuana experience and especially continued use are a rarity. These statistics reflect the fact that the members of the first wave of accelerated marihuana interest are only now reaching their early 30's. There is also evidence, however, that increasing age associated with the assumption of adult roles and adult responsibilities makes marihuana use less practical and appealing. Whatever the diminution of use brought about by new role demands, however, it appears quite likely that there will be some increase in continued

marihuana use among the over-30 group as more of the young adults with histories of cannabis use enter this age group.

While there are areas and groups in which cannabis use may be approaching or has already reached an upper limit, overall use levels may be expected to rise as other groups more recently introduced to marihuana move toward a level of saturated interest. Persistent use for nearly a decade by large numbers, despite significant attempts to discourage marihuana use, suggests that cannabis use is more than a fad and may well prove to be an enduring cultural pattern in the United States.

The amounts and frequency of use in the United States are still quite modest when compared to countries in which cannabis use is more traditional. Use continues to be comparatively infrequent and typically involves relatively low potency material. But there is also evidence that users in significant numbers are beginning to use on a daily basis. For example, among males between 20 and 30, 1 in 6 of those who have ever used marihuana continues to do so on a daily basis. In some locales, as noted in the discussion of the San Mateo County study, regular marihuana use may be nearly as common or even more common than regular cigarette use.

As mentioned earlier, while marihuana use including daily use has decidedly increased in the past decade, the attitudes and behavior of most youth and adults continue to be relatively conservative. Among the high school seniors discussed earlier, nearly three out of four (70 percent) disapproved of <u>regular</u> marihuana use. Half said even were it legal to buy and use, they would not do so. Two out of five high school seniors feel that those who smoke marihuana regularly do so at "great risk of personal harm." With respect to the use of other drugs, a very large majority disapprove of even trying them -- 9 out of 10 disapprove of trying heroin or LSD; 4 out of 5 disapprove of trying uppers or downers.

As was emphasized in earlier reports, many users stop or markedly diminish their use of marihuana as they take on various adult responsibilities such as new marital, parental and work roles (8, 30, 73). Thus, while the future patterns of use of marihuana in our society are in doubt, there is reason for believing that a variety of considerations, including negative attitudes of many potential users toward regular drug use, serve to moderate and discourage more extensive use even when the drug is widely available.

Predicting Marihuana Use

Several studies were published in the past year concerning the prediction of marihuana use based on earlier behavior, personality, belief and attitude indicators. One study (36) found that high school users as compared with non-users placed lower value on achievement and higher value on independence, tended to be more alienated and critical, more tolerant of deviance, less religious, less influenced by parents as compared to friends, and had a lower

grade point average. Moreover, those who initiated marihuana use between their first and second interviews tended to show shifts in the above directions during the interval between contacts.

In a similar study (82), five year longitudinal data were collected for students in grades 4-12. In this study of children and adolescents, rebelliousness was the best predictor of future marihuana use. Non-users tended to describe themselves and to be described by others as obedient, law-abiding, conscientious, trustworthy and hardworking. By contrast, those who became later marihuana users were more likely to be rated as impulsive and less sensitive to the feelings of others; but at the same time, more sociable, talkative and outgoing than non-users. Such ratings were also generally predictive of those more likely to become "early" versus "late" marihuana users.

These high school level studies are reminiscent of college studies reported in previous Marihuana and Health Reports (101, 105) which indicated that college student users tended to be non-conformists when compared to those who did not use. However, as use becomes more typical of the group, the user generally becomes more like his or her peers. It should also be kept in mind that predictors, while useful in anticipating average behavior in a group, are not necessarily usable for individual cases.

Studies of parent-child relationships are of interest in providing some indication of possible influences on use of marihuana and other drugs by children. It has been found that while peer factors are especially important for marihuana initiation, intrapsychic factors and a lack of closeness of family ties are more important in relation to more serious involvement with use of illicit drugs (43).

Given the role that marihuana use has come to play as part of the adolescent and young adult cultures, emergent use often becomes a part of the young person's integration into a social subculture in which drug use is one part.

Many of the factors which have been found to be related to drug use including that of marihuana -- low academic performance, rebelliousness, depression or criminal activity -- appear more often to precede rather than to follow the use of drugs.

CHEMISTRY AND METABOLISM OF CANNABIS

The chemistry and metabolism of cannabis (i.e., the ways in which marihuana is broken down and transformed chemically by the body) are highly technical areas which are of considerable practical importance. Reports in this series have stressed that marihuana is not a single chemical substance. While Δ-9-tetrahydrocannabinol (Δ-9-THC) was identified early as the principal psychoactive ingredient in cannabis, other constituents may be important in modifying the action of THC in addition to having their own physiological implica-

tions. In this respect, marihuana is not like beverage alcohol which is a relatively simple compound.

The detection of marihuana in the human body is an important chemical problem with major legal and research implications. As marihuana comes to be more widely used, it is being used increasingly while driving or under other conditions likely to endanger the user and others. Because Δ-9-THC and other cannabis constituents are rapidly transformed into other chemical substances (metabolites) and because of the very small quantities involved, detection remains a difficult scientific problem.

In 1976, a major monograph on the progress made in developing detection methods was published by the National Institute on Drug Abuse (98). Work is continuing on the development of simple tests, analogous to blood alcohol determinations that might be useful at the site of accidents and in roadside determinations of marihuana intoxication. There are now a variety of techniques suitable for detection by laboratories, although none is reasonably priced or sufficiently simple to be used reliably for this purpose. It still remains to be established, however, that such assays will be useful for law enforcement purposes. To do so will require that there be a demonstrated consistent correlation between the level of intoxification detected and impairment of driving abilities.

Emphasis in chemical research has also been on synthesizing the various naturally occurring cannabis constituents, their biological transformation products or metabolites and related chemical substances. The production of such chemically pure substances provides essential tools for determining possible effects of each constituent alone as well as in combination with other marihuana ingredients.

Availability of these synthetic materials in research quantities can accelerate research on marihuana detection in body fluids as well as other work on the pharmacological effects of marihuana. By radioactively labelling some of the active substances involved, it is possible to trace their passage through the body. Availability of these constituents and related materials also has implications for assessing the possible therapeutic value of cannabis. Since the natural material has some undesirable side effects (e.g., accelerated heart action and an intoxication that is disturbing to some), it would be useful to find related drugs which have the desired therapeutic effect (such as control of nausea for cancer patients or treatment of some forms of glaucoma), but are free from side effects. The synthesis of chemically related substances has the potential of achieving that end.

Some of the metabolites of marihuana are very active in themselves, making an understanding of them important to knowledge of the parent substance. Additionally some constituents can block important drug metabolizing enzymes in the liver (i.e., block natural chemicals which play an essential role in metabolizing drugs or preventing the accumulation of potentially injurious substances). Such blocking

might cause toxic reactions were marihuana to be ingested simultaneously with other drugs normally detoxified in the liver. It is, therefore, important to understand this aspect of marihuana's action.

Tests with dogs (97) and rats (12) revealed that the major marihuana metabolites produced by the lung may be different from those produced by the liver. This suggests that the effects of cannabis may be partly determined by the route of administration (e.g., smoking vs. eating). Similar differences have been reported in humans.

The identification of cannabis metabolites that remain in the body for days following marihuana use (51) was an important development because it paves the way for their synthesis and the careful evaluation of their possible toxic implications.

The finding that there is an interaction between cannabidiol, a major marihuana constituent, and Δ-9-THC, marihuana's principal psychoactive ingredient (53) may ultimately shed light on the common belief among users that different varieties of cannabis with varying composition have different effects only partly related to THC level.

ANIMAL RESEARCH

A considerable amount of animal research on the effects of marihuana continues. Unlike humans, their genetic and learning histories can be accurately specified enabling the researcher to separate the role of marihuana from that of other aspects of life style and development. Their shorter life spans also permit the study of chronic effects over proportionately longer periods of their lives and the use of drug dosages that would not be possible in humans. As in previous years, much of the animal work is primarily of interest to the research specialist; however, some of the behavioral findings are of more general importance.

Marihuana and related drugs have consistently been found to suppress aggression in animals when they are not under stress (1). These findings concur with less systematic human observation which suggests that marihuana is considerably less likely to facilitate the expression of aggression than is alcohol. With animals under stress, however, it has been found that marihuana tended to increase aggression. This suggests that the relationship between marihuana and aggression may be more complex than was earlier supposed. Whether similar results would be obtained with humans in stress situations is not known.

One recent trend in animal behavioral research has been the study of marihuana use in social interaction. In one such experiment reported last year (79, 80) several marihuana-related changes in social behavior of monkeys in three to six member social groups were noted. Given oral doses equivalent to very heavy human cannabis

use, the monkeys responded much like humans. They slept and rested more frequently; active social interaction such as grooming of others was reduced. Over more extended periods of administration, the monkeys gradually showed fewer and fewer of these effects. While aggression was initially reduced, after receiving THC for weeks or months during the year-long study the monkeys became irritable and aggressive (hitting, biting, chasing increased).

Another important area of animal research concerns possible long term, chronic effects of marihuana. Two previously reported studies failed to find any residual effects of Δ-9-THC on learned behavior in rats following discontinuance of the drug after 150 days of use (23) or after seven months of intermittent administration (22). More recently, an impairment in maze learning was found following six months of heavy use (20). Because of the high doses, the relevance of these findings to human experience is questionable. The possibility that heavy doses of cannabis administered during pregnancy might impair learning in the offspring of rats has been raised by one recent study (96). Here, too, the relevance to human use is uncertain. In general, however, it should be emphasized, as in previous editions of this report, that the use of cannabis by pregnant women is especially unwise since the implications of such use in humans have not been adequately explored.

HUMAN EFFECTS

Because many of the effects of marihuana have already been extensively described in previous editions of the Marihuana and Health Report (101, 102, 103, 104, 105) and in other widely available reviews of the literature, this report will be restricted to the developments of the past year. Many of the more recent research publications represent work which has already been discussed in prior years but has only more recently appeared in the scientific literature.

Effects on cardiovascular functioning have been extensively studied. Indeed, tachycardia (an accelerated heart rate) is the most common and prominent physiological response to marihuana use. Previous editions of the Report have stressed evidence that the effects of marihuana may be dangerous for those with cardiac abnormalities. Evidence that marihuana not only increases heart rate, but may also temporarily weaken heart muscle contractions has led the researchers who originally studied patients with heart disease to express concern about marihuana use among individuals with such problems (74). The research on the effects of marihuana on patients with angina (cardiac related chest pain) illustrates that effects on those with any type of health problem cannot always be predicted from studies of normal volunteers. Studies of normal young men have not revealed any serious effects on heart functioning.

A second area which has received considerable research attention in recent years is that of the effect of marihuana on lung functioning. Because marihuana is characteristically smoked in the United States

and because of the known adverse effects of cigarette smoking, this has been a continuing source of concern. The irritating sensation associated with deep inhalation is well known to users and there have been numerous clinical reports of lung and throat irritation. Although there is now good evidence that marihuana and Δ-9-THC administered acutely produce an increase in the diameter of the air passages of the lung (88, 89, 93, 94), chronic use may have quite different implications. Previously reported research (94) has indicated impairments in pulmonary function in chronic marihuana smokers. More recent work (90) using still more sophisticated measures has demonstrated detectable impairment in lung functioning after six to eight weeks of heavy cannabis smoking. The changes found, while still within normal limits, persisted at least one week after smoking. This suggests that heavy chronic use could well lead to clinically important changes similar to those found in heavy cigarette smokers.

Special Health Problem Areas

Several areas of marihuana research findings which were highlighted in previous years have created considerable concern over the possible biological implications of cannabis use. The possible effects involved are:

a. Impairment of the body's natural defense system against disease -- i.e., interference with or depression of the immune response;
b. Chromosomal alterations -- i.e., increases in the number of abnormal chromosomes and a reduction in the number of chromosomes in some body cells;
c. Basic alterations in cell metabolism;
d. Impairment of endocrine functioning; specifically, a reduction in the male hormone testosterone and in growth hormone levels;
e. Brain damage.

Although evidence is fragmentary and incomplete in all of these areas, the potential seriousness of the possible consequences for the individual and society has resulted in great interest and some controversy over the implications of research. If the immune system is impaired by marihuana use, the clinical consequences might include a seriously heightened susceptibility to a wide range of diseases. Changes in chromosomes, the material of genetic transmission, might have serious implications for both the individual and, conceivably, future generations if abnormalities were genetically transmitted. Changes in cell metabolism, specifically in DNA and RNA production which are basically involved in cell reproduction, might have far-reaching consequences. These include the possibility of a failure in cell reproduction and replacement, erratic cell growth or increased cancer susceptibility. Possible impairment of endocrine functioning is also worrisome because it might result in inadequate or incomplete sex differentiation in the male fetus when a mother uses marihuana heavily while pregnant.

Alterations in testosterone and growth hormone in the developing child or adolescent might adversely affect growth and sexual maturation. Finally, gross damage to the brain might have a wide range of behavioral implications. The present state of the research evidence for each of these consequences is outlined below. It should, however, be re-emphasized that the clinical possibilities outlined in the preceding continue to be speculative. There is as yet no good evidence that marihuana smokers do, in fact, develop clinical abnormalities of the type described.

The immune response: Previous Marihuana and Health Reports (104, 105) have discussed in detail earlier research concerning the question of a possible impairment in this health-sustaining bodily response. Two years ago a report indicated that a marked reduction in the immune response as measured in white blood cell cultures was found in marihuana smokers compared to non-smokers (71). This reduction was reported to be comparable to that of patients with known "T-cell" immunity impairment -- uremia, cancer and transplant patients. Attempts to replicate this finding and to explore its implications by testing for immune response depression by other means have resulted in contradictory reports. To further complicate interpretation, it was found that marihuana smokers off the street (i.e., not specifically part of an on-going study) showed a reduction in the type of immune response involving T-cell or thymus dependent lymphocytes (a type of white blood cell involved in preventing disease). This reduction sometimes found in smokers did not, however, persist in users smoking quality controlled marihuana in a closed ward research setting (75). Thus, the reduction in T-cells observed in some chronic drug users may be the result of some common factor of their life style other than marihuana use. The relationship between a reduced number of T-cells and possible diminished immunologic function is also doubtful because other measures of immunologic functioning (various skin tests used to measure the immune response in those who show clinical evidence of diminished response) have not indicated a reduced functioning in marihuana smokers making use of known amounts of marihuana under controlled conditions. A recently published animal study using high, but still humanly relevant doses of inhaled cannabis smoke, found that it had an immune response suppressing effect in rats that justifies further research (108).

Thus, the issue of possible impaired immune response remains unresolved. There is, as yet, no evidence that users of marihuana are more susceptible to such diseases as viral infections and cancer, which are known to be associated with lowered production of T-cells.

Chromosome abnormalities: There is little new evidence to report in this area. While there have been reports of increases in chromosomal breaks and abnormalities in human cell cultures, the results to date are inconclusive. The three positive studies in humans that have been reported (32, 50, 87) have decided limitations. All were retrospective -- i.e., studies of those who had already used marihuana as compared to non-users. Such variables as differences in life style, exposure to viral infections and possible use of

other drugs, all known to affect chromosome integrity, could not be reliably assessed. In two of the studies, the aberrations observed were found only in a minority of the users.

Three other studies done prospectively (i.e., before and after use) have been reported (55, 56, 72). All were negative although they, too, can be faulted for a variety of reasons: most importantly, the subjects of all three had at least some prior experience with marihuana. It is possible that the baseline levels of chromosome deficits may have been elevated by earlier casual marihuana use, thus masking a drug-related effect.

A team investigating the effect of marihuana smoke on human lung cells in laboratory culture has found an increase in the number of cells containing an abnormal number of chromosomes (52). Another investigator who previously reported a high proportion of cells in marihuana smokers with reduced numbers of chromosomes (63) has more recently reported that the addition of Δ-9-THC (the principal psychoactive ingredient of marihuana) to human white blood cell cultures also resulted in an increased frequency of cells with abnormally low chromosome numbers (64). The implications of these recent findings are uncertain.

Overall, there is no convincing evidence at this time that marihuana use causes clinically significant chromosome damage. However, it should be emphasized that the limitations of the research conducted thus far preclude definitive conclusions.

Alterations in cell metabolism: The implications of laboratory findings on the inhibition of DNA, RNA and protein synthesis (all of which are basically related to cellular reproduction and metabolism) are still unknown. In addition to work previously reported, research last year has found that adding Δ-9-THC to various types of human and animal cell cultures inhibits DNA, RNA and protein synthesis (5). This study detected no effect on DNA repair synthesis or in the uptake of the chemical precursors into the cell although the amount of these precursors within the cells was reduced by half.

The possibility that cannabis, or one or more of its chemical ingredients, differentially affects the cell metabolism and reproduction of cancer cells in animals was raised by research of the last two years. One aspect of the mechanism by which this may occur is an inhibition of DNA metabolism in abnormal cells but not in normal cells.

If this preferential inhibition of DNA synthesis in animal tumors also occurs in humans, the potential value of marihuana as an anti-cancer drug will be explored. It should, however, again be stressed that there is presently no evidence that cannabis or any of its synthesized or naturally occurring constituents has definite value in inhibiting human cancer growth. There is also the possibility, again related to cell metabolism, that if animal findings of a depressed cell mediated immunity response are substantiated in

humans, cannabis might assist with transplant surgery.

Endocrine functioning: The Fourth and Fifth Marihuana and Health Reports (104, 105) discussed a reported reduction in blood levels of testosterone in smokers and the contradictory findings. Some of the inconsistency in these findings has been explained by the varying time periods over which these levels were assayed. For example, one chronic study under carefully controlled conditions found there was no significant drop in the level of testosterone during the first four weeks of daily use; however, a drop did occur with continued use (48, 49). In most cases, however, the hormone levels tested still remained well within generally accepted normal limits. One recent report (29) indicates a decreased sperm count in otherwise normal young cannabis smokers that may be related to use. Some differences in the cellular characteristics of sperm of chronic hashish users compared to nonusing controls were reported this year, but their functional significance is unclear (107).

The question of the biological significance of the previously reported alterations in testosterone and growth hormone levels remains in doubt. It may well be that these findings will ultimately prove more significant for individuals with already impaired fertility or other evidence of marginal endocrine functioning than for normal individuals.

Recent reports of reduced testosterone levels of heavy alcohol consumers may make the clinical separation of marihuana and alcohol effects more difficult since both drugs are frequently used by the same individuals.

Brain damage research: A British research report, originally appearing in 1971 (9), attributed brain atrophy to cannabis use in a group of young male users. This report is repeatedly cited in popular articles on marihuana use. In the original study 10 patients, all of whom had varying histories of 3-11 years of marihuana use, were examined by a neurological technique (air encephalography) used to detect gross brain changes. The authors concluded that their findings suggested that regular use of cannabis may produce brain atrophy. This research was faulted on several grounds: all of the patients had used other drugs, making the causal connection with marihuana use questionable; and the appropriateness of the comparison group and diagnostic technique were questionable. The potential seriousness of the original observations did, however, lead to several subsequent studies.

In a study of chronic Greek users (86) a different technique (echoencephalography) was employed to determine whether brain atrophy might be present in heavy users. (Air encephalography was not used because the hazards of that technique were not ethically justifiable for purely research purposes.) The findings from the Greek study were negative; that is, users were not found to differ from non-users in evidence of gross brain pathology.

Most recently two studies have been conducted in Missouri (43) and Massachusetts (58), respectively, of two samples of young men with

histories of heavy cannabis smoking using computerized transaxial tomography (CTT), a brain scanning technique for visualizing the anatomy of the brain. In this technique the head is scanned by a narrow beam of X-rays in a series of "slices." Computer processing of the data obtained from a large number of measurements makes it possible to reconstruct the anatomy of the brain in a more detailed manner and with greater precision than pneumoencephalography (the technique used in the original British study of 1971) permits.

In the St. Louis study 12 young male subjects, aged 20-30 (mean age = 24.1) who had smoked at least 5 joints a day (mean # = 9.0/day) for 5 or more years (mean years = 6.6) were compared to 34 neurologically normal young men of similar age who did not indicate drug use. In the Boston study 19 heavily using young male marihuana smokers, whose use was verified on a closed research ward, were matched with a control series of non-using males of similar age.

In both studies, the resulting brain scans were read blindly by experienced neuroradiologists. In neither study was there any evidence of cerebral atrophy. Despite these negative findings, several additional points should be emphasized. Neither study rules out the possibility that more subtle and lasting changes of brain function may occur as a result of heavy and continued marihuana smoking. It is entirely possible to have impairment of brain function from toxic or other causes that is not apparent on gross examination of the brain in the living organism. Nevertheless, virtually all studies completed to date (late 1976) show no evidence of impaired neuropsychologic test performance in humans at dose levels studied so far.

A retrospective study of an Egyptian prison population in which 850 chronic cannabis users were compared to 839 non-cannabis using controls reported slower psychomotor performance, impaired visual coordination and impaired memory for designs in users (83). This investigator reported that such impairment was more commonly found in subjects from urban backgrounds who were younger and more educated than in illiterate, rural and older subjects (84). While this finding suggests the possibility that findings for chronic users may differ depending on their background, the study has obvious deficiencies. Subjects often used other drugs besides cannabis. The study could not specify the actual levels of use, which may have differed in the several groups. In addition, other aspects of the users' life styles or experiences may have affected the outcomes rather than their cannabis use, as such.

As was reported last year, studies of college students which compared users to non-users have not generally found decrements in intellectual performance as measured by the grades achieved by users. The higher levels of motivation possibly involved in students compared to the general user population, the typically modest levels of use (by overseas standards) and the possible elimination of those impaired by marihuana use at an earlier point in their academic careers, are all limitations to a broad interpretation of these findings.

With respect to brain wave tracing (electroencephalography or EEG) in humans, there is ample evidence that cannabis produces reversible and dose-related changes in brain waves as conventionally measured under conditions of acute administration (24, 47). These are not markedly different from those of other psychoactive drugs. In Greece, studies of chronic users which employed advanced computerized EEG analysis techniques failed to find persistent abnormalities distinguishing a heavy user group from their non-user counterparts (86). However, at least one investigator using deep planted electrodes which measure electrical activity within the brain rather than at its surface has reported persistent changes in monkeys and in a small number of humans (28). Just what, if any, behavioral or functional significance these changes may have is not now known.

Overseas Chronic User Studies

Research on long term, chronic users of cannabis overseas where such use has been characteristic of large numbers for many years continues to be discussed in many contexts without adequate consideration of its many limitations. The older studies of this type suffered from multiple scientific defects making their interpretation difficult. More recently, three studies conducted under Federal aegis in Jamaica (76, 77), Greece (86) and Costa Rica (11) have received considerable publicity. Although they have been discussed in previous years, a review of the findings and their limitations is desirable in order to place them in realistic perspective.

Reports on all three studies have now appeared in the scientific literature (11, 76, 86). In each of the three, considerable effort was made to match chronic users with non-users whose characteristics apart from drug use were quite similar. Such user/non-user matching was rather carefully done in the Jamaican and Costa Rican studies; in the Greek study precise matching was less possible. All subjects were men because male use predominates in the three cultures studied. The elaborate testing procedures limited the total number studied. This is an important limitation since it is possible that the limited sample size may have precluded the detection of rarer consequences of cannabis use. For example, samples of similar sizes of matched cigarette smokers and non-smokers might not have detected some of the known serious consequences of cigarette smoking such as heightened susceptibility to heart disease, lung cancer and emphysema.

A wide range of measures were employed in these studies to detect physical or psychosocial consequences of use. In general, few differences were found that could be directly attributed to cannabis use. In the Greek study, heavy hashish users examined were significantly higher in psychopathology, particularly antisocial personality disorder, but it was not possible to know whether this predisposed them to heavy hashish use or whether use played a role in producing their pathology.

Data on chromosomal assays were collected in Jamaica, and have sometimes been cited as indicating that cannabis use has no chromosomal effects. More accurately, these data must be regarded as inconclusive because of technical deficiencies in the methodology for that phase of the research.

It should again be emphasized that while the results of these studies are somewhat reassuring with regard to grossly adverse consequences of marihuana use, they by no means demonstrate that cannabis use is free of potentially adverse consequences. The small numbers studied, the possibility that cultural differences may have masked drug related performance differences and the differences in the demands of these less industrialized societies from those of our own, all make direct translation of the results to American conditions hazardous. Since adults with long experience in marihuana use were studied, none of the three projects is directly relevant to the implications of marihuana use by American adolescents at an earlier stage of development and under different social conditions.

Psychopathology

Previous editions of the Marihuana and Health Report (102, 103, 104, 105) have discussed at some length the question of possible psychiatric aspects of cannabis use. Probably the most common adverse psychological reaction to marihuana use among American users is the acute panic anxiety reaction (26, 61). It represents an exaggeration of the more usual marihuana response in which the individual loses perspective (i.e., the realization that what she or he is experiencing is a transient drug induced distortion of reality) and becomes acutely anxious. This reaction appears to be more common in relatively inexperienced users although unexpectedly higher doses of the drug can cause such a response in the more experienced as well. Generally the symptoms respond to authoritative assurance and diminish in a few hours as the immediate effects of acute intoxication recede.

Transient mild paranoid feelings are common in users and it has been suggested that those who are characterized by more paranoid defense mechanisms are less likely to experience other acute adverse reactions (68). Earlier it was emphasized that reactions of users are very much influenced by the set and setting of use. Set refers to the pre-existing expectations the individual has regarding use; setting means the physical environment during use. It is generally conceded that anxiety and mild paranoid reactions are more likely if the user is initially anxious about the experience and/or the circumstances of use are anxiety producing. Some additional research support for this clinical impression is found in a field survey which used a questionnaire to measure acute adverse drug reactions (70). Preliminary work has found that, in a college population, those who are more hypochondriacal, and who feel less in control of their own lives and more at the mercy of external events are more likely to have adverse reactions to marihuana and other psychoactive drugs (69).

An acute brain syndrome associated with cannabis intoxication including such features as clouding of mental processes, disorientation, confusion and marked memory impairment has been reported. It is thought to be dose-related (much more likely at unusually high doses) and to be determined more by the size of the dose than by pre-existing personality (61). This set of acute symptoms appears to be rare in the United States, possibly because very strong cannabis materials are less readily available here than in some overseas locations. Acute brain syndrome also diminishes as the toxic effects of the drug wear off.

Descriptions of a specific cannabis psychosis are to be found principally in the Eastern literature (26, 61), from cultures where use is typically more frequent and at higher doses than those generally consumed in the United States. It has been difficult to interpret such reports because diagnosis of mental illness is partly dependent upon socio-cultural factors. In addition, the diagnostic picture is frequently complicated by the use of other drugs and earlier evidence of psychopathology not necessarily associated with drug use. While the recent overseas studies conducted under U.S. auspices in Jamaica, Greece and Costa Rica did not find such adverse consequences, the small size of the user samples studied, together with the probable rarity of the disorder, would have made its detection unlikely.

One recent clinical study in India contrasted the features of a paranoid psychosis arising in the course of long term cannabis use with that of paranoid schizophrenia (91). Twenty-five consecutive patients admitted with each diagnosis were compared. The cannabis users, reportedly, had used the drug for five or more years in amounts up to several grams per day in gradually increasing quantities. Those diagnosed as having a cannabis psychosis were characterized by the authors as showing more bizarre behavior, more violence and panic, an absence of schizophrenic thinking and greater insight into their illness. Patients with the cannabis-related disorder recovered rapidly upon being hospitalized and being treated with a major tranquilizer.

In this and other clinical studies, it is difficult to distinguish the role of cannabis from that of pre-existing psychological problems or other environmental precipitants in marihuana-related psychological difficulties. Frequently, heavy marihuana users are also those who have had emotional problems prior to use.

Marihuana flashbacks — spontaneous recurrences of feelings and perceptions like those produced by the drug itself — have been reported (7). A survey of U.S. Army users recently published found that flashbacks occurred in both frequent and infrequent users and were not necessarily related to a history of LSD use (85). Such experiences may range from the quite vivid recreation of a drug related experience to a mild evocation of a previous experience. The origin of such experiences is uncertain but those who have experienced them appear to have required little or no treatment.

One source of information about possible adverse reactions to drugs, including marihuana, is the Federally sponsored Drug Abuse Warning Network (DAWN). This is a nationwide reporting system which provides information about the frequency with which various drugs in common use are implicated in patient or client contacts with such facilities as hospital emergency rooms and crisis centers. (A crisis center is a facility established to provide "walk in" or "phone in" assistance to those experiencing personal crises, including adverse drug reactions.) Of 118,000 emergency room episodes involving some form of drug abuse between May, 1975 and April, 1976, marihuana ranked 16th among the drugs mentioned. But in crisis center contacts, marihuana ranked second only to heroin as the drug involved. While the interpretation of such figures is made more difficult by ignorance of how the number seeking assistance compares to the total number using a drug during the reference period, it does indicate that marihuana is not an uncommon factor in individuals seeking help.

In the past the Federal Client Oriented Data Acquisition Process (CODAP), a reporting system designed to monitor Federally supported drug treatment programs, found that a significant portion of the effort (more than 10 percent) was being devoted to patients whose primary drug of abuse was marihuana. When it was determined that this was largely an artifact of court and school referrals for administrative convenience, an effort was launched to substantially reduce this inappropriate use of community treatment facilities. As a result of these efforts, between October, 1975 and April, 1976, 3 out of 5 (57 percent) of the inappropriately used treatment slots were freed for patients with more serious problems of drug abuse (this included some slots that were being used for patients reporting alcohol or "no drug" as their basis for referral).

Complex Psychomotor Performance in Driving and Flying

Evidence that marihuana use at typical social levels definitely impairs driving ability and related skills continues to accumulate (17, 33, 65). There are now data indicating impairment from laboratory assessment of driving related skills (19), driver simulator studies (16, 66), test course performance (45), actual street driver performance (46) and, most recently, a study conducted for the National Highway Traffic Safety Administration of drivers involved in fatal accidents (100).

Unfortunately, despite the commonly expressed belief that their driving is impaired by cannabis intoxication, there is reason for believing that more users drive today while intoxicated than was true a few years ago (15, 46, 92). As marihuana use becomes increasingly common and accepted and as the risk of arrest for simple possession decreases, it is likely that more users will risk driving while high. In limited surveys, from 60 percent to 80 percent of marihuana users questioned indicated that they sometimes drive while cannabis intoxicated (45, 46, 81).

Marihuana use in combination with alcohol is also quite common and the risk of the two drugs used in combination may well be greater than that posed by either substance alone.

A recent study of drivers involved in fatal accidents in the greater Boston area was conducted by the Boston University Accident Investigation Team and found that marihuana smokers were over-represented in fatal highway accidents when compared to a control group of non-smokers of similar age and sex (100).

There are, therefore, several converging lines of evidence that driving performance is impaired by marihuana intoxication, viz.: users' subjective assessments of their driving skills while high, measures of driving related perceptual skills, driver simulator and actual driving performance and, finally, a limited study of actual highway fatalities.

The parameters of impairment for the average driver under various dosages of marihuana alone or in combination with alcohol are not yet adequately specified. There is, thus, an obvious need to develop standards in this area for what constitutes driving under the influence of cannabis so as to encourage more responsible use. At present it is clearly desirable to strongly discourage driving while marihuana intoxicated.

As indicated last year, there has been relatively little systematic study of the relationship of marihuana smoking to possible airplane pilot error. Nevertheless, the evidence related to psychomotor skills in driving is partially germane. Such skills as the detection of peripheral visual stimuli and complex psychomotor coordination are at least as important in flying as driving. The inherently greater complexity of flying suggests that pilot performance is even more likely to be impaired while marihuana intoxicated.

The few studies completed to date have all shown that experienced pilots undergo marked deterioration in performance under flight simulator test conditions while high (34, 35, 57, 99). Although more detailed studies of pilot performance while under the influence of marihuana are desirable, flying an aircraft while marihuana intoxicated is obviously hazardous.

A continuing danger common to both driving and flying is that some of the perceptual or other performance decrements resulting from marihuana use may persist for some time (possibly several hours) beyond the period of subjective intoxication. Under such circumstances, the individual may attempt to fly or drive without realizing that his or her ability to do so is still impaired although he or she no longer feels high.

Tolerance and Dependence

Tolerance to cannabis -- diminished response to a given repeated drug dose -- has been substantiated by research evidence cited in

the Fifth Report (105). Tolerance development was originally suspected because experienced overseas users were able to use large quantities of the drug that would have been toxic to U.S. users accustomed to smaller amounts of the drug. Carefully conducted studies with known doses of marihuana or THC leave little question that tolerance develops with prolonged use (3, 13, 41, 59, 60).

As was pointed out last year, the meaning assigned to cannabis dependence is often vague. If it is defined as a manifestation of physical symptoms following discontinuance of the drug, there is experimental evidence that it can occur at least under conditions of extremely heavy research ward administration that would be atypical of U.S. use patterns (3, 21, 41). The changes noted following drug withdrawal under these experimental conditions include: irritability, restlessness, decreased appetite, sleep disturbance, sweating, tremor, nausea, vomiting and diarrhea. Some of these symptoms were experienced in a similar research study by users who selected their own smoked marihuana doses (60). Such a "withdrawal syndrome" is uncommon and has rarely been reported clinically. Only one research report, from Germany, has noted it (106).

THERAPEUTIC ASPECTS

A significant part of the new biology of marihuana research has been the revival of interest in its possible therapeutic value. As earlier editions of these reports have indicated, cannabis has an ancient history of medicinal use which has persisted in the folk medicine of many countries.

While there have been no new therapeutic applications of cannabis or of its synthesized constituents recently, there has been some additional research on earlier cited applications. One of the more promising medicinal uses is based on the observation that in both normals and in patients suffering from glaucoma, marihuana serves to reduce intraocular pressure (31). Δ-9-THC shows definite promise of becoming an effective agent for the management of glaucoma. An eye drop preparation has been developed and is currently undergoing testing in animals preliminary to human trials. Such a preparation has been successfully employed with rabbits (25).

A second area that continues to show promise is the use of Δ-9-THC as a means of reducing or eliminating the nausea, vomiting and loss of appetite in cancer patients following chemotherapy (75). Since present anti-emetics are often unsuccessful in controlling such symptoms in these patients, an improved treatment for this purpose would be desirable.

A third area in which marihuana research has shown promise of developing improved treatment methods is in the management of asthmatics. Synthetic Δ-9-THC produces a desirable temporary increase in the size of the air conducting passages. Facilitating breathing in these patients (94, 95). While the natural material

has a similar effect, it is undesirable because it also has a direct irritant effect on lung tissue. There are some indications that persistent smoking of marihuana itself, like cigarette smoking, may lead to lung pathology (cf., Human Effects).

A book published during 1976 reports on a conference on the therapeutic potential of marihuana and serves as a detailed summary of the work of researchers in this area (14).

Despite the promise that marihuana and/or its synthesized constituents have shown as potential therapeutic agents, it should once again be emphasized that much additional work is necessary before such agents become generally approved as standard medications.

Marihuana and its constituents continue to have adverse side effects. The increase in heart rate produced is obviously undesirable with the elderly or the cardiac impaired. The psychological effects recreationally sought by many are often disturbing and disruptive to patients.

If consistently useful medical applications for marihuana are found, it is quite likely that the product or products resulting will be chemically related but not identical to the natural material's constituents. Cannabis, which was used therapeutically earlier in Western medicine for a variety of reasons, was eventually abandoned because of such problems as variable potency -- it often ranged from being inert to being much more powerful than the prescriber intended -- and undependable shelf life.

Whether or not cannabis, one of its synthesized constituents or a chemically related compound once again finds a place in modern medicine depends on several considerations. One problem is that pharmaceutically desirable effects may not be persistently useful for chronic disorders. Tolerance undoubtedly develops for a number of the effects of the natural material. This may also be true for new chemically related compounds. Like any other new medication, chemically related materials must be carefully tested for toxicity and for therapeutic effectiveness. This process is time consuming and many new pharmaceuticals showing initial promise are ultimately discarded as unanticipated drawbacks and limitations arise.

FUTURE RESEARCH DIRECTIONS

Cannabis research has made impressive progress since the inception of priority emphasis in the late 1960's. We have become increasingly sophisticated in areas as diverse as the chemical characteristics of the material and the psychosocial implications of use. Some of what has been learned has served to allay many of the emotionally based fears of the past. While it now appears that i[illegible]quent, experimental use at typical U.S. levels is usually without significant hazard, more frequent, and especially chronic use, may have quite different implications.

Despite some popular assertions to the contrary, much remains to be learned about this drug which has come to play an increasingly important role in the life of American youth. Our studies of chronic use are decidedly limited and are surely insufficient guides to the implications of use by large numbers of Americans. There is an obvious need to study larger samples more carefully to determine the impact of cannabis use on health and the psychosocial functioning of users. Such long-term studies preferably beginning before use and continuing over extended periods are now possible in the United States although the planning and launching of this research is a major undertaking. Because once a large scale longitudinal study is launched, it is often not possible to modify it without compromising the research, planning must be especially painstaking. Such planning is now underway.

Adequately specifying the parameters of risk posed by marihuana is a difficult task. Obviously, it is important to know with some precision what levels of marihuana intoxication pose threats in such areas as highway safety and the operation of potentially hazardous machinery. Since marihuana is often used in conjunction with alcohol and a wide range of less common over-the-counter and prescriptive drugs, it is also important to know under what circumstances significant interactions occur. There has been a range of research concerning biological consequences in such areas as the immune response, endocrine functioning and basic cell metabolism. While there are some who are inclined to dismiss some of the more disquieting results as artifactual and without significant clinical implications, it is important that they be followed up and the issues they raise resolved.

Unlike many other drug substances, marihuana's metabolites tend to be relatively persistent with residuals remaining in the body fat for days or even weeks. This has led to concern that even irregular use might have inadequately foreseen consequences if any of the more serious laboratory findings of possible hazard prove to be clinically significant. Here, too, more must be learned.

Changes in social policy concerning marihuana that have now occurred in eight states provide a kind of natural laboratory for determining some of the impacts of law and social policy on use patterns. A better understanding of use patterns and their implications for functioning may enable us to develop means of discouraging all forms of drug abuse including that of marihuana without resorting to primarily legal measures.

The rise in use among adolescents has generated concern about possible consequences of use in this group especially when such use becomes an escape from the demands of preparing for later life. Some progress has been made in identifying those in this age group who are likely to become more heavily involved with marihuana use. A better understanding of the motivations for heavy use may permit the development of means for early intervention to avert possible life-long patterns of drug dependency.

Although marihuana use does not "cause" other drug use in the way once simplistically believed, it is often associated with other drug use. Exploration of preventive approaches which encourage individuals to avoid patterns of drug dependency (both licit and illicit) is needed.

Progress in the marihuana research program has made us aware that as our knowledge has increased so has our awareness of our need for more subtle understanding of marihuana use and its possible implications.

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